This correlated with the observation that, initially, the area under stimulation became considerably oedematous; response enhancement was therefore demonstrated satisfactorily only in the erythematous surround of the oedema.

Recording were also made of the activity of 11 single units isolated in 'few-fibre' preparations. When electrical stimulation at A-fibre levels was applied to the nerve distal to the sites of recording, it resulted in their activation. In addition, the slight bending of a hair by the stimulating stylus was sufficient stimulus for their maximal firing; these units were therefore assigned as hair-follicle units with myelinated fibres[6]. After PGE_2 injection 8 such units yielded higher numbers of impulses per stimulus delivery (figure 2); 2 units showed fewer impulses and the activity of a further unit remained unaltered.

Discussion. The present experiments have shown that the subdermal injection of PGE_2 leads to increased sensory input as judged by the multi-fibre activity in a peripheral nerve evoked by a standard tactile stimulus. Prostaglandins of the E series are thought to be released in the skin following the kind of noxious stimulation that gives rise to inflammation[8]; inflammation pain as well as PGE-induced hyperalgesia can be explained as the outcome of receptor sensitization by PGEs[1,9]. Nociceptors possess small myelinated or unmyelinated fibres. Handwerker[9] has demonstrated the sensitizing effects of PGE_2 on unmyelinated nociceptor fibres; we have demonstrated the sensitization of myelinated as well as unmyelinated fibres, some of which subserve tactile sensation whilst others are implicated in nociception. Such sensitization may well be a contributing factor to the inadequately understood hyper-aesthesic properties of the area of secondary hyperalgesia (tenderness) surrounding the focus of an inflammatory lesion[10].

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Lesions in the substantia nigra of rats induce thermoregulatory deficit in the cold[1]

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Summary. Rats with either electrolytic or chemical (6-hydroxydopamine) lesions in the substantia nigra displayed decreased metabolism and hypothermia when they were exposed to cold (8 °C T_a), although they showed no deficiency in thermoregulation at both moderate (22 °C) and hot (30 °C) environmental temperatures.

It is well known that the nigrostriatal dopamine (DA) pathways are one of the 3 main types of DA pathway in the brain[2-4]. The nigrostriatal DA fibres originate from cell bodies in the substantia nigra (SN). These fibres ascend through the lateral and mid-hypothalamus, and fan out to innervate the neostriatum. In addition, it is now well established that in Parkinson's disease, there is a characteristic pattern of both cell loss in the substantia nigra and DA decrease in the striatal nuclei[5,6]. Further, it has been suggested that patients with Parkinson's syndrome show a thermoregulatory deficit[7]. We have, therefore, investigated the effects of both electrolytic and chemical (6-hydroxydopamine, a depletor of catecholaminergic nerve fibres) lesions to the SN on the metabolic, respiratory and vasomotor activities as well as body temperature responses of rats at various ambient temperatures (T_a), in order to determine the nature of the contribution that the nigrostriatal DA pathways might make to thermoregulatory control.

Materials and methods. Adult male Sprague-Dawley rats weighing between 250 and 300 g were used in all experiments. The animals were housed individually in wire-mesh cages in a room maintained at 25 ± 2.0 °C. The animals were given free access to tap water and granular feed. In preparation for the SN lesions, the animals (under the general anesthesia of sodium pentobarbital, 6 mg/100 g, i.p.) were placed in a Kopf stereotaxic instrument and prepared with bilateral electrolytic destruction of the SN (pars compacta) on the animal's left and right sides, according to the atlas of König and Klippel[8]. The following coordinates and current parameters were used: AP, −2.4, L, −1.6, and H, −2.6; 2 mA for 10 sec, anodal current. The electrode used to produce lesions was stainless steel insulated with teflon except for 0.5 mm at the tip. In preparation for chemical lesions, using the same stereotaxic techniques, an aliquot containing 1 µl of 6-hydroxydopamine (6-OH-DA, Sigma, 50 µg) was slowly infused via a 27-gauge stainless steel cannula (with the outer diameter of 0.45 mm) into the SN pars compacta. 2-3 weeks after the operation the animals were tested for thermoregulatory activity in a small partitional calorimeter. Metabolic rate (M) was calculated from the animal's oxygen consumption. Metabolic rate was calculated in W assuming an RQ = 0.83 so that 1 l of oxygen consumed per h was equivalent to a heat production of 5.6 W[9,10]. Respiratory evaporative heat loss (E_{res}) was calculated by measuring the increase in water vapor content in the helmet effluent air over that of the ambient air. Evaporative heat loss expressed as W was calculated from evaporative water loss assuming the latent heat of vaporisation of water to be 0.7 W/h/g of water[9,10]. Rectal (T_r), foot skin (T_f), tail skin (T_t) and back skin (T_{bsk}) temperatures were measured using copper-constantan thermocouples. Measurements were obtained every min as a d.c. potential with a Hewlett-Packard digital voltmeter (DVM 3455) interfaced online to a CPU Hewlett-Packard 9825 computer which calculated temperatures, M and E_{res} and relayed them on an online Hewlett-Packard 9871

printer. Upon termination of the experiments the animals were anesthetized with a overdose of sodium pentobarbital. Then, the caudate-putamen complex was dissected out of the brain for the biochemical assay of DA contents. The residual portion of the brain containing the SN was fixed in a 10% formalin solution and was sectioned on a freezing microtome. The sections were stained with thionin to facilitate lesion localization.

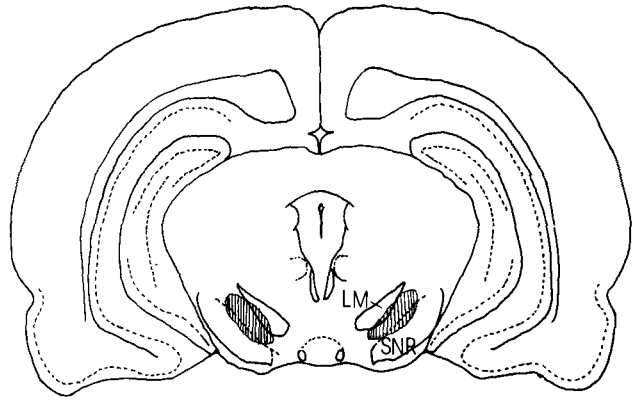
Results and discussion. On the basis of experimental treatment and histological results, the animals were grouped into 1 of the following 5 categories: I) non-lesion controls (n = 6), II) sham-lesion controls (n = 7) consisted of rats that were surgically manipulated in the same way that experimental groups were treated except that no electrical current was passed, III) acceptable, electrolytic lesions to the SN (n = 8) involving substantial or complete loss of pars compacta somata in addition to minimal extra-compacta damage (figure), IV) unacceptable, electrolytic lesions to the SN (n = 7) producing only minimal or incomplete loss of pars compacta with major extra-compacta damage, and V) SN lesions produced by 6-OHDA (n = 9). A biochemical assay of the corpus striatum revealed that only the lesions restricted almost exclusively to the pars compacta (as shown in the group of acceptable, electrolytic SN lesions) produced a severe, almost complete reduction (92%) of DA content in the caudate-putamen complex (table 1).

Table 1. Effects of both electrolytic and chemical lesions to the substantia nigra (SN) on dopamine content of rat corpus striatum[a]

Treatment	Striatal dopamine contents (ng/g)
Non-lesion controls (6)	804 ± 85.1
Sham-lesion controls (7)	778 ± 74.3
Unacceptable, electrolytic lesions to the SN (7)	537 ± 67.9[b]
Acceptable, electrolytic lesions to the SN (8)	59 ± 18.4[b]
6-Hydroxydopamine (50 µg, intra-SN) lesions to the SN (9)	168 ± 34.6[b]

[a] The chemical assay of dopamine content in the striatal nuclei was carried out by the methods reported previously[9].
[b] Significantly different from control value (non-lesion controls), p-value less than 0.05 (1-way analysis of variance). The values are expressed as the mean ± SEM, followed by the numbers of rats in parentheses.

Both the experimental and control groups of animals were kept for 90 min at each level of T_a to attain thermal balance before thermoregulatory data were collected. The responses to each level of T_a (8, 22 and 60 °C) were calculated by averaging 30-min consecutive determinations of each thermoregulatory parameter, taken 1 min apart. Mean skin temperature (T_s) was calculated from the equation: $T_s = 0.83\ T_{bsk} + 0.10\ T_r + 0.07\ T_t$[11]. Table 2 contains a summary of the mean and SE values for each of the measured and calculated parameters collected from the 5 groups of animals at each of the 3 T_a used. Both rats with sham lesions and rats with unacceptable, electrolytic lesions to the SN maintain rectal temperature and other thermoregulatory parameters within the normal limits displayed by the non-lesion controls. On the other hand, rats which received either acceptable, electrolytic lesions or 6-OHDA lesions to the SN, although showing no alterations in resting T_r, T_s, M and E_{res} at both 22 and 30 °C T_a, did display a lower T_r, a lower T_s and a lower M than the non-lesion controls at 8 °C T_a. In fact, it has been repeatedly documented that electrolytic and 6-OHDA lesions to the SN produced DA depletion in the corpus striatum of rat brain[12–15]. The present results also showed that substantial loss of pars compacta DA somata (induced by electrolytic lesions) and intra-SN



Localization, on selected section of the rat's brain, of SN-lesioned sites which produced a thermoregulatory deficit in the cold (8 °C T_a) (shadow area in oblique lines). The section is from König and Kippel[8]. Abbreviations: LM, medial lemniscus; SNR, substantia nigra, pars reticulata.

Table 2. Thermoregulatory responses of control rats, rats with electrolytic lesions to the substantia nigra (SN), and rats with 6-hydroxydopamine (6-OHDA) lesions to the SN to different ambient temperatures (T_a) of 8, 22 and 30 °C. Metabolic rate (M), respiratory evaporative heat loss (E_{res}), mean skin temperature (T_s) and rectal temperature (T_r) were measured when the animals were in the thermal balance at each T_a

	Treatment of animals	T_a (°C)	T_r (°C)	T_s (°C)	M (W/kg)	E_{res} (W/kg)
1	Non-lesion controls (6)	8	36.9 ± 0.22	28.8 ± 0.33	8.0 ± 0.25	0.17 ± 0.03
2	Sham-lesion controls (7)	8	36.7 ± 0.24	28.6 ± 0.36	7.9 ± 0.23	0.15 ± 0.04
3	Unacceptable, electrolytic lesions to the SN (7)	8	36.4 ± 0.26	28.2 ± 0.41	7.5 ± 0.31	0.14 ± 0.03
4	Acceptable, electrolytic lesions to the SN (8)	8	34.4 ± 0.27[a]	27.3 ± 0.32[a]	5.5 ± 0.31[a]	0.17 ± 0.03
5	6-OHDA lesions to the SN (9)	8	35.1 ± 0.25[a]	27.5 ± 0.28[a]	6.2 ± 0.33[a]	0.14 ± 0.03
6	Non-lesion controls (6)	22	37.1 ± 0.29	32.6 ± 0.59	5.3 ± 0.26	0.33 ± 0.04
7	Sham-lesion controls (7)	22	37.3 ± 0.34	32.8 ± 0.64	5.1 ± 0.27	0.35 ± 0.05
8	Unacceptable, electrolytic lesions to the SN (7)	22	36.9 ± 0.35	32.3 ± 0.55	4.9 ± 0.24	0.32 ± 0.04
9	Acceptable, electrolytic lesions to the SN (8)	22	37.1 ± 0.33	33.1 ± 0.58	4.9 ± 0.29	0.31 ± 0.04
10	6-OHDA lesions to the SN (9)	22	37.5 ± 0.29	33.2 ± 0.61	4.6 ± 0.25	0.29 ± 0.05
11	Non-lesion controls (6)	30	38.4 ± 0.17	35.5 ± 0.33	4.2 ± 0.14	0.75 ± 0.05
12	Sham-lesion controls (7)	30	38.2 ± 0.15	35.6 ± 0.37	4.0 ± 0.13	0.72 ± 0.06
13	Unacceptable, electrolytic lesions to the SN (7)	30	38.8 ± 0.22	35.9 ± 0.36	3.8 ± 0.15	0.77 ± 0.06
14	Acceptable, electrolytic lesions to the SN (8)	30	38.3 ± 0.22	35.1 ± 0.28	3.7 ± 0.17	0.69 ± 0.05
15	6-OHDA lesions to the SN (9)	30	38.1 ± 0.24	35.4 ± 0.33	3.8 ± 0.16	0.68 ± 0.04

[a] Significantly different from corresponding control value (non-lesion controls), $p < 0.05$ (1-way analysis of variance). The values are expressed as the mean ± SEM, number of rats in parantheses.

injection of 6-OHDA (50 µg), respectively, produced a 92% and a 80% reduction of striatal DA contents. Thus, the present evidence is in favor of the involvement of the nigrostriatal DA pathway in thermoregulation. Specifically, severe loss of pars compacta somata or substantial depletion of striatal DA contents lead to a thermoregulatory deficit in the rat in the cold (8 °C T_a). In addition, it has been shown that the depletion of extra-central noradrenaline levels with systemic administration of either 6-OHDA or alpha-methyl-p-tyrosine[11,16,17], surgical sympathectomy[18] and immunosympathectomy plus adrenal demedullation[19] caused an impairment in adaptability to changes in cold environmental temperatures. It is not known whether the nigrostriatal DA depletions result in an inhibition in both heat production and heat loss mechanisms in the cold via a reduction of the extra-central noradrenaline level or a reduction in preganglionic sympathetic outflow in the rat. In this situation, the decreased rate of cutaneous heat losses could not effectively counteract the impaired M, which led to hypothermia.

Finally, it must be acknowledged that electrolytic lesions destroy more tissue than only the pars compacta DA neurones. In addition, the high amount of 6-OHDA (50 µg) must have destroyed non-dopaminergic neurones in the neighborhood. However, the present results showed that unacceptable, electrolytic lesions to the SN produced no deficiency in thermoregulation accompanied by a slight reduction (33%) of striatal DA contents. This indicates that thermoregulatory deficit is specifically correlated with nigral DA neurones. Our recent findings also showed that the apomorphine-induced hypothermia was not enhanced by pretreatment with 6-OHDA[20]. Therefore, the supersensitivity of the residual dopamine can be ruled out in the present experiments as mediating the observed deficiency in thermoregulation.

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Control of muscle insulin receptors by the motor nerve*

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Summary. I^{125} insulin binding and the uptake of oxygen and 2-deoxyglucose are increased in skeletal muscle after denervation, suggesting an increase in insulin receptors (IR). Sustained increases in the number of affinity of IR molecules may account for some properties of denervated muscle fibres.

Muscle denervation is followed by a well-known sequence of metabolic and electrophysiological changes, including an increase of glucose and amino acid uptake[1,2], more rapid protein turn-over[3], increased calcium binding by sarcolemma and sarcoplasmic reticulum[4,5], greater contractile responses to agents causing an increase in intrafibre calcium ($[Ca^{++}]$)[6-8], as well as partial depolarization[6,9], a rise in transmembrane resistance[6,9,10], reduction of potassium and chloride permeabilities (pK^+, pCl^-)[11-13], and an increase in pNa^+ [14]. There is also a remarkable spread of acetylcholine receptors (AchR) over the muscle surface[8,15-17]. Though it may initially gain weight[18], the muscle then atrophies. With the exception of depolarization and atrophy very similar changes can be produced by exposing the muscle to insulin[19-27]. We have therefore examined the effects of denervation on the insulin receptor (IR) of skeletal muscle and find that interruption of a muscle's nerve supply is followed by an increase in either the hormone binding affinity or the number of IR sites on the membrane. To estimate the number and activity of insulin-receptor complexes on muscle we have measured insulin binding (I^{125} insulin), labelled hexose uptake (^{3}H-2 deoxyglucose), oxygen consumption ($\dot{V}o_2$) and resting membrane potential (RMP) in experiments on normal or denervated soleus (SOL) or extensor digitorum longus (EDL) muscles of young, adult (75-125 g), male Wistar rats. For the insulin binding studies only SOL was used, the preparation being essentially the same as that of Le Marchand-Brustel et al.[28]. The muscles were washed for 1 h after removal and incubated 2.5-7 h in the nutrient solution of Bretag[29] with 2% BSA (fraction V, Sigma, St. Louis, MO, USA) and I^{125} insulin (New England Nuclear, Boston, MA, USA, sp. act. ~100 µCi/µg) in a final concentration of 2.5 ng/ml, or 0.4×10^{-9} M. To estimate non-specific binding, a normal or denervated muscle of similar weight from another animal was simultaneously incubated in the same solution, to which was